REMARKS

Applicant hereby requests further consideration of the present application in view of the amendments above and the comments that follow. This Amendment is responsive to the Final Official Action of September 20, 2007 ("the Action"). Claims 43-88 and 105-123 are pending in the application (new dependent Claim 124 has been added).

I. The §112, First Paragraph Written Description Rejections

Claims 43-51, 54-88, 105, 106, 108-116 and 119-123 stand rejected under §112, first paragraph as allegedly failing to comply with the written description requirement. The Action opines that the claims contain subject matter, which was not described in such a way as to "reasonably convey" to one skilled in the relevant art that the inventor(s) had, at the time the application was filed, possession of the claimed invention.

A. The "at least about 400 nm" recitation.

The Action rejects the wavelength recitation of "about 400 nm" because the claims do not include an upper range of either 660 nm (original Claim 52) or about 900 nm (p. 40, line 7). Applicant respectfully submits that the claimed wavelength is not "more broad" than the originally described ranges. Para. 127 of the specification states that "any particular wavelengths are for exemplary purposes only" and the embodiments of the present invention are not limited by these examples.

However, independent Claims 43, 105 and 119 have been amended to add in the recitation "to about 900 nm" to obviate this issue and advance prosecution. Claim 114 has been amended to recite an excitation range of between about 630-660nm (p. 39). Accordingly, Applicant respectfully requests that these rejections be withdrawn.

B. The "a source other than the sensor" recitation.

The Action rejects Claims 43-88 and 105-116 for the phrase "a source other than the sensor" (as recited for example, in line 13 of Claim 43). The Action says the specification specifically provides support for "an internally administered analyte" (systemically or locally, etc…) at paragraph 57. Action, p. 4. Applicant believes that this description and the specification and figures <u>clearly</u> support that the fluorescent analyte is administered from a source other than the sensor. Applicant respectfully submits that this feature has sufficient written description support. One of skill in the art reading the specification would clearly understand that the inventors had possession of the claimed invention. As such, Applicant submits that there is no new matter introduced by this recitation. Examples of support are restated below.

Pages 38-39 of the application state:

> In some embodiments according to the present invention, a fluor from an exogenous source can be used. In such cases, the fluor signal can be used to quantify the amount of labeled analyte in the tissue or it can monitor for the activation or extinction of the fluor signal due to some cellular or natural process. The value of this signaling capability is that it may identify events like antigen expression changing, apoptosis setting in and the like. Some embodiments, according to the present invention, may also include a matrix for release of a fluor-labeled antibody held on the sensor body, <u>but the sensor may be configured without such a matrix and be configured to project excitation light and detect the illuminated fluorescence in response thereto based on the presence of a fluor-labeled analyte</u> such as a labeled antibody that are externally administered. (emphasis added)

Pages 12-13 of the application states:

> As used herein "internally administered" refers to introducing an analyte or substance, systemically and/or locally, into a subject by whether ingesting the analyte, topically applying the analyte, providing the analyte intravenously, inhaling the analyte, injecting the analyte and the like. Although embodiments of the present invention are primarily discussed herein with respect to fluorescently labeled analytes (fluor-labeled analytes), other embodiments of the present invention are not limited to this configuration. As discussed above, naturally fluorescent analytes and/or analytes that exhibit fluorescence when introduced (ingested, inhaled, intravenous, injection, topical) to a subject may also be used without

departing from the teachings of the present invention.

Applicant submits that one of skill in the art would recognize that Applicant was in possession of the claimed invention based at least upon the above descriptions as the application reasonably conveys this feature. For example, the description at pp. 38-39 clearly states that the sensor can be configured without a matrix on the sensor body ... such as a labeled antibody that is externally administered (external of the sensor), *e.g.*, internally administered via a systemic or local delivery or administration as described at pp. 12-13. However, in order to more clearly recite the claimed feature, Applicant has amended Claim 43 to recite, that "the fluorescent analyte is internally administered from a source other than the at least one sensor." Applicant submits that this recitation is supported by the application as filed and provides a clear understanding of the claimed feature. Applicant has amended Claim 105 to recite that the fluorescent analyte is systemically administered. Accordingly, Applicant respectfully requests that these rejections be withdrawn.

C. The "at least 2 mm" recitation.

The Action also extends a new matter rejection for the recitation of "at least 2 mm" in Claims 44, 45, 60-64 and 105 because this exact distance was not found in the specification. However, page 35, lines 1-5 indicate that the sensor is configured to project excitation light through localized tissue so that light penetrates through layers of fascia that may encapsulate the sensor and that testing has shown that a laser diode can penetrate approximately 20 mm. Page 38 also states that sensors can probe activity at subsurface locations in tissue that is **several millimeters** away (typically up to about 20 mm away) and may pass through any thin layer of fascia that may be present. Applicant respectfully submits that the term "several" millimeters means more than one millimeter. Thus, Applicant respectfully submits that there is sufficient support of the term " at least 2 mm."

However, Applicant has amended Claims 44 and 105 to recite either that the

excitation light is projected to probe activity at locations away from the sensor so that the light penetrates layers of fascia that may encapsulate the sensor and/or through fibroblasts having thicknesses of between about 50-100 μm (p. 35, p. 38) and/or to recite that the sensor can probe subsurface activity in tissue that is "several millimeters" away from the sensor, to advance prosecution. *See also*, Figures 9A, 9B, which illustrate exemplary excitation light penetration depths of several millimeters. Applicant respectfully requests that these rejections be withdrawn.

D. The "devoid of a coating that has fluorescence capability" and/or "uncontrolled sample volume" recitations.

The Action also rejects Claims 115 and 116 for the "negative provisio" phrase "devoid of a coating that has fluorescence capability" and the phrase "the sensor detects fluorescent analyte in local tissue in an uncontrolled sample volume." Applicant agrees that there are no literal statements for these features. However, Applicant also submits that one of skill in the art would clearly understand that the inventors had possession of the claimed invention based on the original application, which describes a sensor that detects systemically or locally administered analytes (*e.g.* the sensor does not have a fluor matrix or coating). As such, the sensor body inherently does not have an integral fluorescent matrix that reacts with chemicals or emits fluorescence.

Rather, as described in the original application, embodiments of the instant invention are directed to monitoring dynamic activity in tissue away based on a remotely internally administered analyte. Such a configuration is very different than a reactive sensor or a sensor that provides the fluorescence. Further, the sensor detection is clearly done using an uncontrolled sample volume, by exciting a volume of local tissue locally but away from the sensor body and receiving signal in response thereto. Such a configuration allows for dynamic monitoring of biochemical activity that allows for pharmacokinetic analysis that is not provided by the cited prior art.

As acknowledged by the Examiner, the specification does describe that that the sensor may (or may not) include a biocompatible coating (such as Parylene C) configured so that the

fluorescence excitation and response light is transmittable through the sensor wall (para. 10), clearly this description of the coating supports the claimed subject matter. The sensor is configured (with or without any coating) so that the fluorescence excitation and response light are transmittable through the sensor wall to and from a volume of local tissue. *See, e.g.*, para. 104, 105, 110. The coating is not required to enhance the fluorescence transmission nor provide the fluor. For example, as described at p. 35 of the application:

> In certain embodiments, the fluorescence sensor or probe **10** will be configured to project excitation light through localized tissue so that the light penetrates through layers of fascia that may be encapsulating the sensor **10**. Testing has shown that a laser diode can produce light that penetrates approximately 20 mm through tissue with some trade-off in intensity due to tissue attenuation. Testing on nude mice has also shown that the catheter-based fluor-sensor and excitation light source can also be used to generate excitation light that penetrates to a depth of many millimeters. Thus, biofouling associated with chronic implantation of the sensor **10** should not inhibit operation of the device with respect to signal intensity since the laser light will penetrate layers of adsorbed proteins and lipids and will transmit sufficiently through muscle, blood, serum, etc.

Thus, while Applicant reiterates that the uncontrolled volume and coating recitations are sufficiently supported, to advance prosecution, Claim 115 has been amended to state that the at least one sensor has a wall surface that <u>is configured to allow excitation and response light to be transmittable through the sensor wall</u> and that the sensor <u>excites and</u> detects fluorescence from the fluorescent analyte in local tissue <u>through a layer of fibroblasts and/or fascia encapsulating the sensor</u> caused by a patient's foreign body bioreaction after sensor implantation (*see, e.g.*, pp. 35, 38)

Claim 116 depends from Claim 43 and Applicant did not find the objected to recitations in Claim 116.

Applicant believes that the claims have sufficient written support. However, if the Examiner finds that the amendments or arguments do not overcome the rejections under Section 112, Applicant solicits the Examiner's suggestions as to satisfactory amendment.

II. The Substantive Art Rejections

The Examiner rejects the pending claims as being obvious over U.S. Patent App. Publication 2002/0102212 to Black ("Black I") in light of U.S. Patent 7,096,053 to Loeb ("Loeb") alone or in combination with U.S. Patent 6,330,464 to Colvin et al. and US 2004/0054385 to Lesho.

A. Claims 43-55, 60-63, 70-77 and 105-123 stand rejected as being obvious over Black I and Loeb.

The Action states that Black I teaches methods of providing labeled antibodies *in vivo* to tissue having antigens that specifically bind a fluorescently labeled antibody using implantable telemetric sensors. The Action concedes that Black I does not teach a 400 nm excitation light, but opines that Loeb teaches that this wavelength is well known and alleges it would have been obvious to modify Black I to operate as taught by Loeb.

First, Applicant respectfully submits that even combined, Black I and Loeb fail to teach or suggest the claimed systems. Black I includes a sensor <u>with an integral matrix</u> or material that releases or creates the fluorescent material locally.

Loeb proposes a percutaneous optical fiber probe (inside a box) <u>with a reaction surface</u> with narrow dimensions and limited sensing ability and appears to function to generate a "spot biopsy" rather than a volumetric detection with a larger field of view provided by the instant invention. The use of the optical fiber of 50-200 μm would limit the area and volume of light transmission. Loeb also proposes to use a pore size to selectively allow diffusion of analytes into the matrix (col. 4, lines 53 *et seq.*). Loeb describes using <u>a chemical reaction between the analyte and the biosensing material **116**</u> (col. 5, lines 27-28, col. 9, line 63) *e.g.*, a biomolecule (col. 10, line 8) or whole cells (col. 10, line 34) are immobilized in the biosensing matrix. Loeb states that where fluor is bound via antibody to analyte, the materials of the containment matrix are selected to be permeable to the analytes being detected but not to the reporting molecule (col. 11-12, lines 65-5).

In contrast, embodiments of the instant invention provide sensors that detect fluorescent activity in local tissue that can monitor pharmacokinetic activity based on

exogenous materials. <u>Stated differently, sensors of the instant invention can "passively" monitor (*e.g.*, "watch" or image) dynamic activity in local tissue, such as, for example, a biokinetic, pharmacodynamic or pharmacokinetic response to internally administered fluor-analyte, as described at pp. 4, 30 and original Claims 25, 30 and Figures 6-8, 13A-13E. The monitoring is based on a volume of tissue outside the fascia zone. The sensors are configured to "watch" rather than perturbate the local environment as proposed by prior art sensors, such as those that release the fluorescent material from the sensor body and/or that induce or require a local chemical reaction or uptake the analyte in an integral biosensing material or matrix</u>. Applicant believes that the sensors of the instant invention can provide more sensitive dynamic data of actual bioactivity. The independent claims are restated below for ease of discussion.

> 43. A detection system for detecting fluorescence in a body of a subject associated with an administered fluorescent analyte, the fluorescent analyte including at least one of a fluor-labeled analyte, a naturally fluorescent analyte and an analyte that exhibits fluorescence when administered to the subject, the detection system comprising:
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> at least one fluorescence sensor configured for *in vivo* operation, the at least one sensor comprising at least one excitation light source held therein, the excitation light source being configured to emit a fluorescent excitation light signal used to generate a fluorescent response of the fluorescent analyte in local tissue, <u>wherein the sensor projects the excitation light signal outside the sensor at a distance sufficient to probe fluorescent activity at locations away from the sensor of several millimeters</u>, with the fluorescent excitation light signal having a wavelength that is at least about 400 nm to about 900 nm, and to detect fluorescence from the fluorescent analyte in the local tissue in the body in response to the emitted excitation light signal, at least intermittently, over a period of time extending for at least about 24 hours after administration of the fluorescent analyte to the subject, <u>wherein the fluorescent analyte is internally administered from a source other than the at least one sensor</u>; and
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> a processor operably associated with the at least one sensor configured to direct the output of the excitation signal and to receive fluorescence intensity signal data associated with the detected fluorescence of the administered analyte in response to the excitation light signal at the fluorescence excitation wavelength from the at least

one sensor, wherein said processor is configured to monitor intensity of the detected fluorescence over time and determine at least one of the following: a pharmacokinetic, a pharmacodynamic, or a biokinetic response to the internally administered fluorescent analyte and/or local bioactivity based on the monitored intensity over at least one monitoring period.

105. A detection system for detecting fluorescence in a subject associated with an administered fluorescent analyte, the fluorescent analyte including at least one of a fluor-labeled analyte, a naturally fluorescent analyte and an analyte that exhibits fluorescence when internally administered to the subject, the detection system comprising:

at least one implantable fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit an excitation light signal having a fluorescent excitation wavelength of at least 400 nm to about 900 nm at a depth into local tissue at a tumor treatment site in the subject's body so that the excitation light penetrates layers of fascia that may encapsulate the sensor and/or through fibroblasts having thicknesses of between about 50-100 μm and to detect fluorescence from a fluorescent analyte in the local tissue beyond the layers of fascia in response to the emitted excitation light signal, wherein the at least one sensor can probe fluorescent activity at subsurface locations in the local tissue that is several millimeters away from the sensor, at least intermittently, over a period of time extending for at least about 24 hours after administration of a fluorescent analyte during each monitoring period, and wherein the sensor is configured to detect fluorescence from a fluorescent analyte that is systemically administered; and

a processor operably associated with the at least one sensor configured to direct the output of the excitation signal and to receive fluorescence intensity signal data associated with the detected fluorescence in the local tissue from the at least one sensor, wherein said processor is configured to monitor intensity over time associated with one or more of the uptake and retention of the fluorescent analyte in the local tissue at a plurality of points in time over at least one monitoring period.

117. A detection system for detecting fluorescence in a patient's body associated with an administered fluorescently labeled chemotherapeutic agent, the detection system comprising:

at least one implantable fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit a fluorescence excitation light signal between about 400 nm to about 900 nm and to detect fluorescence from a fluorescently labeled chemotherapeutic agent in localized tissue in the body in response to the emitted excitation light

signal, at least intermittently, over an active monitoring period of time extending for at least about 24 hours after administration of the fluorescently labeled chemotherapeutic agent, wherein the at least one sensor is dormant between successive active monitoring periods; and

wherein said processor includes computer readable program code for monitoring fluorescence intensity over time of the detected fluorescence associated with one or more of the uptake and retention of the fluorescently labeled agent in target localized tissue at a plurality of points in time over at least one monitoring period, and wherein the processor includes computer readable program code that calculates a dose of the chemotherapeutic agent in the localized tissue and/or that determines a patient's likely therapeutic response to the chemotherapeutic agent based on the detected fluorescence.

119. A detection system for monitoring pharmacokinetics and/or pharmacodynamics in a subject associated with an administered fluorescently labeled analyte, the detection system comprising:

at least one fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit a fluorescence excitation light signal at a wavelength of at least about 400 nm to about 900 nm and to detect fluorescence from the fluorescently labeled analyte in localized tissue at a target site in the body in response to the emitted excitation light signal; and

a processor operably associated with the at least one sensor configured to direct output of the excitation signal to the target site and to receive the detected fluorescence intensity signal data, wherein said processor is configured to monitor fluorescence intensity of the fluorescently labeled analyte in the localized tissue at a plurality of points in time over at least one monitoring period and determine the pharmacokinetics and/or pharmacodynamics at the target site.

123. A system for determining a phenotypic response of a patient to a selected drug therapy, comprising:

at least one fluorescence sensor configured for *in vivo* operation, the at least one sensor being configured to emit a fluorescence excitation light signal at a wavelength of at least about 400 nm to about 900 nm and to detect fluorescence from an internally administered fluorescently labeled therapeutic agent in localized tissue at a target site in the body in response to the emitted excitation light signal; and

a processor operably associated with the at least one sensor configured to direct output of the excitation signal to the target site and to receive the detected fluorescence intensity signal data, wherein said processor is configured to monitor fluorescence intensity of the fluorescently labeled therapeutic agent in the localized tissue at a plurality

> of points in time over at least one monitoring period and predict a phenotypic response of the patient to the therapeutic agent at the target site.

Applicant respectfully submits that, even combined, Black I and Loeb fail to teach or suggest at least the emphasized features. Indeed, Applicant respectfully submits that Black I and Loeb teach away from the passive operation of the sensor, as each employs a matrix or biosensing material releases the fluors and/or that interacts with the local tissue, *e.g.*, Black I releases labeled antibodies locally from the integral matrix on the sensor and Loeb uses a biosensing material.

The Action alleges that certain claimed features are "intended use" recitations that have not been give patentable weight because the claims are product claims. (Action, pp. 9-10). The Action states that the product claims are examined based on their structural elements (*e.g.*, processor or sensor), not on what type of analyte is to be detected. Applicant respectfully disagrees.

If one were to attempt to use either the sensor of Black I or the system of Loeb to detect an internally administered fluorescent analyte, the detection would either not work or would be incorrect as the local antibody release of Black I would interfere with the "normal" dynamic activity of the fluor-analyte in local tissue, and the uptake in the biosensing material of Loeb would also be problematic the small field of view of the optical fiber would make detection difficult, it at all, and would not allow for monitoring the local biokinetic or pharmacokinetic activity of the labeled analyte in subsurface locations away from the sensor. That is, Loeb does not allow for probing into local tissue because its penetration depth and power, as well as detection are limited by the small diameter optical fibers. For a device such as that proposed by Loeb, that states that it should be placed in a well vascularized area, it would appear that one would need to place the device directly on a vein to obtain the optical signal. Thus, Applicant submits that the noted recitations are not merely "intended use" but structural and operational features that technically define over the cited prior art.

Regarding the Action's statement that the "configured to" language of the processor was not given patentable weight, Applicant respectfully submits that recitations, such as

"configured to" that require steps be performed do limit claims to a particular structure. In particular, the present claims clearly recite operations to be carried out by the processor, which does impart a structure to the processor circuit.

The MPEP states that when functional descriptive material is recorded on some computer-readable medium (*e.g.*, "processor"), it becomes structurally and functionally interrelated to the medium and will be statutory in most cases since use of technology permits the function of the descriptive material to be realized. MPEP 2106.01 (emphasis added). Applicant submits that while this guideline is provided with respect to computer related statutory analysis, Applicant submits that it provides support for Applicant's position that a processor with claimed functional descriptive material provides structure and function and that such must be given patentable weight.

For example, Claim 123 recites that the processor is configured to monitor fluorescence intensity of the fluorescently labeled therapeutic agent in the localized tissue at a plurality of points in time over at least one monitoring period and predict a phenotypic response of the patient to the therapeutic agent at the target site. This claim recitation requires that the processor operate in a certain manner to generate a certain output.

The "method" steps of the analyte administration route (*e.g.*, from a source other than the sensor) is related to the function of the sensor and is NOT merely a method step that has no impact on the function of the sensor as described above with respect to the cited prior art and the integral matrix or biosensing material.

Applicant respectfully submits that the basis for the rejections is flawed as established case law provides that **a processor that is programmed to provide a particular function is structurally different than other processor circuits that are programmed to provide a different function**. For example, *Application of Noll*, 545 F.2d 141, 148 (CCPA 1976), held that "[t]here is nothing abstract about the claimed invention. It comprises physical structure, including storage devices and electrical components uniquely configured to perform specified functions through the physical properties of electrical circuits to achieve controlled results. **Appellant's programmed machine is structurally different from a machine without that program." (emphasis added).**

Also, *In re Lowry*, 32 F.3d 1579, 1583-84 (Fed. Cir. 1994) held that the programmed operations of a processor defines a structure:

> In Lowry's invention, the stored data adopt no physical "structure" per se. Rather, the stored data exist as a collection of bits having information about relationships between the ADOs. Yet this is the essence of electronic structure. In *Bernhart*, this court's predecessor noted:
>
>> There is one further rationale used by both the board and the examiner, namely, that the provision of new signals to be stored by the computer does not make it a new machine, i.e. it is structurally the same, no matter how new, useful and unobvious the result.... To this question we say that **if a machine is programmed in a certain new and unobvious way, it is physically different from the machine without that program; its memory elements are differently arranged**. The fact that these physical changes are invisible to the eye should not tempt us to conclude that the machine has not been changed.
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> *Bernhart*, 417 F.2d at 1400 (emphasis added).

More than mere abstraction, the data structures are specific electrical or magnetic structural elements in a memory.

The Action states in several places with respect to the pending claims that because the claims are product claims, the configured to language has not been given patentable weight because "the intended use" must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Because the cited art teaches a processor in conjunction with a sensor, any processor would be "capable of being configured to perform the claimed (intended use) functions." *See, e.g.*, Action, p. 10-11.

However, by the logic applied by the Action, an unprogrammed processor circuit would anticipate any claimed processor circuit that is programmed to perform a specific task because there would allegedly be no structural difference between the unprogrammed processor circuit and the programmed processor circuit. Processor circuits are naturally defined by their function, not by an apparatus type structure. Accordingly, contrary to

assertions in the Action, the programmed operations do recite structural features that must be given patentable weight.

Moreover, established case law provides that an assertion that the prior art is **capable** of some function is not sufficient without an explanation (from the Examiner) regarding **how** the prior art elements perform each claimed function even though the prior art is structurally different. For example, in *Ex Parte Tomoyuki Kida*, 1997 WL 33102864, *1 (BPAI 1997), the court held that:

> In the instant case, the examiner has not explained how the prior art elements might be capable of performing each of the claimed functions that appear at least in independent Claims 1, 6, and 9. The assertion on page 4 of the Answer that the functions are "inherent" in the prior art because the prior art structures are capable of "performing algebraic calculations" is inconsistent with the law of our reviewing court. See *In re Lowry*, 32 F.3d 1579, 1583-84, 32 USPQ2d 1031, 1035 (Fed. Cir. 1994) (claim limitations regarding organization of data in memory held to distinguish over prior art). See also *In re Alappat*, 33 F.3d 1526, 1545, 31 USPQ2d 1545, 1558 (Fed. Cir. 1994)(commenting that prior cases held that computer, once programmed, creates a new machine); *In re Noll*, 545 F.2d 141, 148, 191 USPQ 721, 726 (CCPA 1976) ("[The claimed invention] comprises physical structure, including storage devices and electrical components uniquely configured to perform specified functions through the physical properties of electrical circuits to achieve controlled results. Appellant's programmed machine is structurally different from a machine without that program.") (emphasis added).

Respectfully, the "intended use" rationale relied on by the Action is incorrect for the same reasons described above, as functional claim language does impart structural distinctions. By way of another example, *WMS Gaming, Inc. v. International Game Technology*, 184 F.3d 1339, 1348 (Fed. Cir. 1999), held that:

> **The structure of a microprocessor programmed to carry out an algorithm is limited by the disclosed algorithm. A general purpose computer, or microprocessor, programmed to carry out an algorithm creates "a new machine, because a general purpose computer in effect becomes a special purpose computer once it is programmed to perform particular functions pursuant to instructions from program software."** *In re Alappat*, 33 F.3d 1526, 1545, 31 USPQ2d 1545, 1558 (Fed.Cir.1994) (en banc); see *In re Bernhart*, 57 C.C.P.A. 737, 417 F.2d 1395, 1399-1400, 163 USPQ 611, 615-16 (CCPA

> 1969) ("[I]f a machine is programmed in a certain new and unobvious way, it is physically different from the machine without that program; its memory elements are differently arranged."). **The instructions of the software program that carry out the algorithm electrically change the general purpose computer by creating electrical paths within the device. These electrical paths create a special purpose machine for carrying out the particular algorithm.** [FN3]
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> FN3. A microprocessor contains a myriad of interconnected transistors that operate as electronic switches. See Neil Randall, Dissecting the Heart of Your Computer, *PC Magazine*, June 9, 1998, at 254-55. The instructions of the software program cause the switches to either open or close. *See id.* The opening and closing of the interconnected switches creates electrical paths in the microprocessor that cause it to perform the desired function of the instructions that carry out the algorithm. *See id.* (emphasis added).

Finally, Applicant respectfully directs the Examiner's attention to the recent Decision on Appeal of Application Serial No. 10/005,889 (*e.g.*, Black I or US 2002-0102212). Briefly stated, the Board of Patent Appeals and Interferences ("the Board") found that the word "configure" means "design, arrange, set up or shape with a view to specific applications or uses." The Board states that the reading of "configured to" is not to be read as "capable of" and not intended use. The Board also found with the Applicant that a processor that is programmed to provide a particular function is structurally different than other processor circuits that are programmed to provide a different function.

In view of the foregoing, the recited operations performed by the claimed processor do provide structure and should be given patentable weight, and Applicant respectfully submits that the claims are patentable over the cited prior art.

B. Claim 48

The Action alleges that the recitation of "a plurality of sensors" is obvious as it is prima facie obvious to combine two compositions known to be useful for the same purpose to form a third composition for the same purpose stating that the idea of combining them flows logically from their having been individually taught.

Applicant respectfully disagrees.

Claim 48 recites the use of at least first and second sensors located in spatially separate locations. This is not the situation of combining compositions, rather using two separate sensors at two different *in vivo* sites. Because embodiments of the invention monitor tumor treatment site, the use of more than one sensor provides additional data regarding the treatment or tissue. In some embodiments, one sensor may be placed at the tumor treatment site and another may be placed in normal tissue close to the tumor site or at a sensitive position.

However, Applicant has amended Claim 48 to recite that the system is configured to monitor fluorescence detected by each of the first and second sensors to provide data for assessing a treatment to clarify the claimed subject matter. Applicant respectfully submits that Claim 48 is patentable over the cited prior art.

C. The alleged inherency of the light depth based on Loeb

The Action alleges that the recitation that the light is able to penetrate at least 2 mm to about 20 mm away is interpreted to be inherent in Loeb because Loeb uses the same wavelength of light and is operated at the same power so that, in absence to information to the contrary, the Action considers that the excitation light of Loeb would inherently have the same properties. Applicant respectfully disagrees.

Loeb uses a percutaneous system with a biosensing element that is inside the body and a relatively long optical fiber that terminates outside the body and with a light source that resides outside the body. Applicant believes that Loeb proposes that the optical fiber is encapsulated by the biosensor material **116** or in close proximity thereto (Loeb, col. 5, lines 28-45). The excitation light travels a longer distance and is optically manipulated before reaching the biosensing element (material) which is the target, there is no need to project beyond this closely spaced target nor to project the light outward over a larger volume of tissue as provided by sensors of the present invention (*see, e.g.,* **Figures 9A, 9B**).

Applicant also submits that Loeb does not teach a specific wavelength range. Loeb proposes several wavelength ranges for exemplary purposes but also states that other wavelength ranges may be used (col. 6, line 55). In light of this "general" discussion of many different ranges, Applicant submits that Loeb fails to provide any enabling teaching on how to achieve the light penetration provided by embodiments of the instant invention. Applicant submits that Loeb claims (see, e.g., Claims 1-9) a biosensing material directly at the end of the optical fiber or transmitting member, which does not appear to require any significant depth of light penetration and also appears to teach that the biosensing material needs to be very close to the optical fiber in order to maximize the fluorescence excitation/emission (Loeb, Figure 1, elements 102, 116). Loeb proposes an optical fiber with a 50-200μm diameters (Loeb, col. 6, line 8), which Applicant submits would decrease the excitation surface area and, hence, the light transmission relative to the instant invention due to the physics of light projection of the tip of the fiber. The small diameter would also apparently limit the detection area and greatly reduce the total incoming fluorescence signal for evaluation/processing.

Also, Loeb describes an active biosensing element, which appears to require fluorescence excitation/emission within a controlled "artificial" setting. Likely due to the biosensing element, the tip of the percutaneous implant of Loeb must be placed in a well-vascularized area (col. 13, line 19). Also, such a probe would have a finite lifetime given its dependency upon chemical reactions or receptor binding.

Applicant respectfully submits that one of skill in the art would not have modified the references to arrive at the claimed invention absent the teachings of the instant invention. Loeb is a percutaneous "near surface" implant and Black I has an integral fluor-matrix. If somehow combinable, such an implant would include an optic fiber to transmit the signal into the integral fluor matrix of the implanted sensor. Applicant reiterates that one of skill in the art would not have modified the cited references in the manner alleged and that the claims are patentable over these references.

D. The Action rejects Claims 43-88 and 105-123 as being obvious over Black I in light of Loeb, in further view of U.S. Patent No. 6,330,464 to Colvin et al. ("Colvin") and U.S. Patent App. Publication No. 2004/0054385 to Lesho ("Lesho").

The Action concedes that Black I fails to disclose that the excitation light is pulsed and other optical circuit features, but cites Colvin and Lesho as teaching optical sensors with such features and alleges that one of skill in the art would have modified the sensor of Black I as modified by Loeb based on the teachings of Colvin and Lesho "because it is well known ...that pulsed excitation light is used in similar implantable fluorescence sensors." Action, p.13. Applicant respectfully disagrees.

First, as noted above, Black I and Loeb fail to teach or suggest the claimed invention. Further, Colvin and Lesho propose an <u>integral</u> encapsulating matrix and are configured to detect light from that matrix (*see, e.g.*, Figures 1- 4 of Colvin and Figures 6 and 7 of Lesho). As such, their proposed optical systems are technically different from that proposed by the instant invention and teaches away from the sensors of embodiments of the invention, which detect light at subsurface locations at millimeters away from the sensor body. In addition, as noted by the Action, Lesho proposes <u>a 50% duty cycle</u>. In contrast, *see, e.g.*, Claims 77 and 78.

As recently noted by the U.S. Supreme Court in *KSR International Co. v. Teleflex Inc., et al.* (550 U.S. 1, 12 (2007)), when the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be non-obvious. In addition, the U.S. Supreme Court also recently noted that a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *Id.* at 14. The Action's reference to four different prior art patents/patent application publications combined to render the claimed invention obvious appears to fall into an improper (hindsight) analysis.

Indeed, Applicant respectfully submits that many of the dependent claims stated to be obvious based on these four references recite novel and non-obvious features. For example, as noted at pp. 39, 40, the sensor can be operated at low duty cycles to detect signal which

may "bleach" out the fluor at higher duty cycle/power levels as the fluorescent analyte is in the local tissue (not on the sensor body). Certain of the optical circuit claims are restated below for ease of discussion[1].

Claim 70 recites a cylindrical filter (which includes semi-cylindrical configurations, *see, e.g.*, p. 40)

Claim 72 recites that the sensor has an optical window formed on the wall thereof to allow the excitation light to exit the sensor through the cylindrical filter.

Claim 73 recites that the sensor includes a compound filter aligned with the excitation light source and formed about a portion of the cylindrical filter to allow the excitation light to exit the sensor through the cylindrical filter.

Claim 74 recites that the light source is positioned in the sensor body proximate the cylindrical wall at a distance and position that directs the excitation light out through the cylindrical filter at an angle greater than the critical angle to thereby allow the excitation light to exit the sensor through the cylindrical filter.

Claim 75 recites that the sensor comprises at least one internal optical filter and a detector configured to detect fluorescence at predetermined wavelengths of interest, and wherein the at least one internal optical filter resides in the sensor body directly over the detector.

Claim 76 recites that the sensor comprises a detector without a filter that detects light that reenters the sensor while the at least one detector is in communication with a filter and detects the fluorescent light at the wavelengths of interest, and wherein the system is configured to monitor unfiltered intensity light. (*see, e.g.*, p. 38).

Claim 77 recites that the sensor is configured to output a plurality of excitation light signals at a pulse duration in a millisecond range and detect fluorescence locally in response thereto over desired intervals over at least 24 hours for each monitoring period.

Claim 78 recites that the sensor includes an anti-reflectance layer in the sensor body intermediate the wall of the sensor body and the underside of the detector.

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[1] *See also*, Claims 51-69, which Applicant submits also recited patent feature, some of which are similar to features discussed with respect to one or more of Claims 70-88.

Claim 79 recites that the sensor comprises a laser diode that is operated in a pulsed manner at a frequency between 10-1000 times per second to generate the excitation light.

Claim 80 recites that the pulsed laser diode is operated between at a frequency of between about 10-1KHz with a duty cycle of between about 1-10%.

Claim 81 recites that the sensor is configured to generate a plurality of excitation signals having a predetermined stepwise variation in intensity, and wherein the detected fluorescence generated in response thereto is used to generate optical profiling data.

Claim 83 recites that the sensor is configured to allow fluorescence to enter and engage with the detector, with the detector having a width that is between about 1.15 R to about 0.54 R, where "R" is the radius of the cross-section of the sensor body.

Claim 84 recites that the cylindrical filter extends substantially continuously over the perimeter of the sensor body at a length that is less than the length of the sensor body .

Claim 85 recites that the sensor further comprises a second detector.

Claim 86 recites that the first and second detectors are held in side-by-side alignment in the sensor body.

Claim 87 recites that first and second detectors are held in back-to-back alignment.

Claim 88 recites that the excitation source comprises first and second diode lasers operating at different excitation wavelengths and/or power.

Applicant respectfully submits that the claimed optical features are patentable over the cited art.

Further, even combined the references fail to teach or suggest features of other claims rejected on this combination of references. For example, a few exemplary claims will be noted below, but Applicant respectfully directs the Examiner's attention to the recitations of Claims 105-123.

Claim 108 recites that the processor is configured to analyze the detected intensity over time and predict whether a subject will have a favorable response to a cancer therapy.

Claim 110 recites that the processor is configured to monitor the intensity over time to confirm antibody attachment to a target tumor site.

Claim 112 recites that the processor is configured to calculate a dose of a

chemotherapeutic agent received at local tissue based on the intensity data intensity over time based on a correlation with *a priori* reference data.

Claim 113 recites that the processor is configured to predict a bioresponse to a chemotherapeutic agent received at the local tissue based on the detected intensity over time.

Claim 117 recites that the processor includes computer readable program code that calculates a dose of the chemotherapeutic agent in the localized tissue and/or that determines a patient's likely therapeutic response to the chemotherapeutic agent based on the detected fluorescence.

Claim 123 recites that the processor is configured to predict a phenotypic response of the patient to the therapeutic agent at the target site.

Applicant respectfully submits that even combined, the references fail to teach or suggest at least the emphasized features. Thus, in view of the above, Applicant respectfully submits that the claims are patentable over the cited prior art.

III. Black I and Statement of Common Ownership

Dr. Robert Black is the sole inventor of Black I and a co-inventor of the instant application ("Black II"). Black II was, at the time the invention was made, owned or subject to an obligation of assignment to the same person (Sicel Technologies) as Black I. Accordingly, there was common ownership with Black I at the time the invention of Black II was made.

Black I has an earlier priority date than Black II. Black I published on August 1, 2002. The instant application was filed on February 17, 2004, but has an earliest effective priority filing date of February 19, 2003, which is less than a year after the publication date of Black I. Thus, Black I is not 102(b) art to Black II. Applicant respectfully submits that Black I is disqualified under 35 USC 103(c) as 102(e) prior art in a rejection under 103(a). *See* MPEP 706.02(l)(1), 706.02(l)(2) and 706.02(m).

Applicant also does not believe that Black I is 102(a) prior art as Dr. Robert Black is the sole inventor of Black I. 35 USC 102(a) states that a person shall be entitled to a patent unless:

> the invention was known or used ***by others*** in this country, or patented or described in a printed publication in this or foreign country, before the invention thereof by the applicant for patent.

According to *In re Katz,* one's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar under 102(b). *In re Katz*, 215 USPQ 14, 17, (CCPA 1982). Thus, there appears to be some question as to whether Black I is 102(a) art. *See, In re Land and Rogers*, 151 USPQ 621, 632 (CCPA, 1966). However, the real issue appears to be whether Black I (with a sole inventor), evidences knowledge *by others* prior to the invention of Black II because Black II names one other inventor.

Applicant respectfully submits the above-information for the Examiner's consideration. However, Applicant believes the claimed invention to be patentable over Black I and the other cited prior art, without removing Black I as a prior art reference, for the reasons discussed above.

CONCLUSION

Accordingly, Applicant submits that the present application is in condition for allowance and the same is earnestly solicited. The Examiner is encouraged to telephone the undersigned at 919-854-1400 for resolution of any outstanding issues.

Respectfully submitted,

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CERTIFICATION OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4) to the U.S. Patent and Trademark Office on December 6, 2007.

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